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EXAMINER	
LU, FRANK WEI MIN	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,873	KOPRESKI, MICHAEL S.	
	Examiner	Art Unit	
	FRANK W. LU	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,17-23,25,28-34,45,46,49 and 50* is/are pending in the application.

4a) Of the above claim(s) *3,7,10,11,19,21,22,30-34,49 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8,9,12,14,17,18,20,23,25,28,29,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on March 31, 2008 has been entered. The claims pending in this application are claims 1-12, 14, 17-23, 25, 28-34, 45, 46, 49, and 50 wherein claims 3, 7, 10, 11, 19, 21, 22, 30-34, 49, and 50 have been withdrawn due to the restriction requirement and species election mailed on October 18, 2007 and April 21, 2006. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on March 31, 2008. Therefore, claims 1, 2, 4-6, 8, 9, 12, 14, 17, 18, 20, 23, 25, 28, 29, 45, and 46 will be examined.

Election/Restrictions

2. This application contains claims 31 and 32 drawn to an invention nonelected with traverse in the reply filed on November 13, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

3. Claim 2 or 6 is objected to because of the following informalities: (1) "A method" should be "The method"; and (2) "human blood plasma or serum" should be "the human blood plasma or serum".

4. Claim 5 is objected to because of the following informality: "non-cellular fractions blood from a human group or population" in step c) should be "a non-cellular fraction blood from a human group or population".

5. Claim 45 or 46 is objected to because of the following informality: "cancer " should be "a cancer".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Scope of enablement

Claims 2, 6, 45, and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a product amplified from total extracellular RNA from plasma or serum of a human, does not reasonably provide enablement for performing the methods recited in claims 2, 6, 45, and 46 wherein the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum can indicate that the disease is any kind of neoplastic disease, the disease can be any kind of neoplastic disease when a tumor-associated RNA species in human blood plasma or serum is overexpressed, and the human can be determined to have any kind of cancer when the RNA species determined in plasma or serum or a non-cellular fraction of blood from the human is a tumor-associated RNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of detecting a human RNA species from blood plasma or serum from a human wherein the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum indicates that the disease is a neoplastic disease, a method of detecting a human RNA species from a non-cellular fraction of blood from a human wherein the disease is a neoplastic disease when a tumor-associated RNA species in the human blood plasma or serum is overexpressed, and a method for comparing an amount or concentration of an extracellular human RNA species present in plasma or serum or a non-cellular fraction of blood from a human to said RNA species present in plasma or serum or a non-cellular fraction of blood from a group or population of humans without cancer wherein the human can be determined to have cancer when the RNA species determined in plasma or serum or a non-cellular fraction of blood from the human is a tumor-associated RNA. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.,* 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Claim 2 encompasses a method of detecting a human RNA species from blood plasma or serum from a human wherein the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum indicates that the disease is any kind of neoplastic disease, claim 6 encompasses a method of detecting a human RNA species from a non-cellular fraction of blood from a human wherein the disease is any kind of neoplastic disease when a

tumor-associated RNA species in human blood plasma or serum is overexpressed, and claim 45 or 46 encompasses a method for comparing an amount or concentration of an extracellular human RNA species present in plasma or serum or a non-cellular fraction of blood from a human to said RNA species present in plasma or serum or a non-cellular fraction of blood from a group or population of humans without cancer wherein the human can be determined to have any kind of cancer when the RNA species determined in plasma or serum or a non-cellular fraction of blood from the human is a tumor-associated RNA.

Working Examples

The specification provides working examples (see pages 24-26) for detecting tyrosinase RNA in serum from normal human and a human with malignant melanoma and for detecting c-abl RNA in serum from human.

The Amount of Direction or Guidance Provided and The State of The Prior Art

Although the specification teaches to detect tyrosinase RNA in serum from normal human and a human with malignant melanoma and detect c-abl RNA in serum from human (see the specification, pages 24-26), the specification does not provide a guidance to show that the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum indicates that the disease is any kind of neoplastic disease as recited in claim 2, the disease is any kind of neoplastic disease when a tumor-associated RNA species in the human blood plasma or serum is overexpressed as recited in claim 6, and the human can be determined to have any kind of cancer when the RNA species determined in plasma or serum or a non-cellular fraction of blood from the human is a tumor-associated RNA as recited in claim 45 or 46.

Furthermore, there is no experimental data in the specification to support the claimed invention. During the process of the prior art search, the examiner has not found any prior art which is related to claimed invention.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum can indicate that the disease is any kind of neoplastic disease as recited in claim 2, the disease can be any kind of neoplastic disease when a tumor-associated RNA species in the human blood plasma or serum is overexpressed as recited in claim 6, and the human can be determined to have any kind of cancer when the RNA species determined in plasma or serum or a non-cellular fraction of blood from the human is a tumor-associated RNA as recited in claim 45 or 46. Furthermore, there is no experimental data in the specification to support the claimed invention. First, since the claims do not require that neoplastic disease is a specific cancer and it is known that 5T4 is highly expressed in both breast and lung cancers (see Table II in page 92 from Southall et al., Br. J. Cancer, 61, 89-95, 1990) and 5T4 mRNA can be detected in both breast and lung cancer patient serum (see page 172, abstract from Kopreski et al., Annals of the New York Academy of Science, 945, 172-178, 2001), when the amplified product or signal of 5T4 mRNA, or cDNA therefrom produced from plasma or serum or a non-cellular fraction of blood of a woman, is detected in an amount or concentration greater than a reference amount or concentration for 5T4

mRNA or cDNA therefrom determined from plasma or serum or a non-cellular fraction of blood of a human group or population without said disease, based on above experimental results, it is unclear how a skilled artisan can determine that the woman is a human with breast caner and is not a human with lung cancer or the woman is a human with lung caner and is not a human with breast cancer. Second, since it is known that hnRNP-A2/B1 is highly expressed in pancreatic tissues from smokers and pancreatic adenocarcinomas (see page 215, abstract from Yan-Sanders et al., Cancer Letters, 183, 215-220, 2002), when the amplified product or signal of hnRNP-A2/B1 mRNA, or cDNA therefrom produced from plasma or serum or a non-cellular fraction of blood of a human, is detected in an amount or concentration greater than a reference amount or concentration for hnRNP-A2/B1 mRNA or cDNA therefrom determined from plasma or serum or a non-cellular fraction of blood of a non-smoking human group or population without said disease, based on above experimental results, it is unclear how a skilled artisan can determine that the human is a human with pancreatic adenocarcinomas and is not a smoking human or the human is a smoking human and is not a human with pancreatic adenocarcinomas. Third, since it is known that Her-2/neu can be detected in human breast cancer but has no expression in Hodgkin and non-Hodgkin lymphoma (see page 574 from Bairey et al., Arch Pathol. Lab Med., 126, 574-576, 2002), overexpression of Her-2/neu in a human blood plasma or serum can not indicate that the human has Hodgkin or non-Hodgkin lymphoma

With above unpredictable factors, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether the overexpression of a tumor-associated extracellular RNA species in the human blood plasma

or serum can indicate that the disease is any kind of neoplastic disease as recited in claim 2, the disease can be any kind of neoplastic disease when a tumor-associated RNA species in human blood plasma or serum is overexpressed as recited in claim 6, and the human can be determined to have any kind of cancer when the RNA species determined in plasma or serum or a non-cellular fraction of blood from the human is a tumor-associated RNA as recited in claim 45 or 46.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working example related to the claimed invention and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 2, 4-6, 8, 9, 12, 14, 17, 18, 20, 23, 25, 28, 29, 45, and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 is rejected as vague and indefinite because it is unclear that a human RNA species in step (c) is identical to a human RNA species in step b) or not. If a human RNA species in step (c) is identical to a human RNA species in step b), a human RNA species in step (c) should be "the human RNA species". Furthermore, the phrase "said RNA species or cDNA therefrom is detected in an amount or concentration greater than the reference amplified product or signal of said RNA species or cDNA therefrom extracted from blood plasma or serum from a human group or population without said disease" does not make sense since said RNA species or cDNA therefrom and the reference amplified product or signal of said RNA species or cDNA therefrom extracted from blood plasma or serum from a human group or population without said disease are different materials and are not comparable. Please clarify.

11. Claim 2 is rejected as vague and indefinite. Since claim 1 is not directed to a method for detecting a disease and does not amplify a tumor-associated extracellular RNA species in human blood plasma or serum, it is unclear why the overexpression of a tumor-associated extracellular RNA species in human blood plasma or serum can indicate that the disease is a neoplastic disease. Please clarify.

12. Claim 4 or 8 is rejected as vague and indefinite because it is unclear that the amplified product means amplified product in step b) or reference amplified product in step c). Please clarify.

13. Claim 5 is rejected as vague and indefinite because it is unclear that a human RNA species in step (c) is identical to a human RNA species in step b) or not. If a human RNA species in step (c) is identical to a human RNA species in step b), a human RNA species in step (c) should be "the human RNA species". Furthermore, the phrase "said RNA species or cDNA

therefrom is detected in an amount or concentration greater than the reference amplified product or signal of said RNA species or cDNA therefrom extracted from non-cellular fractions of blood from a human group or population without said disease" does not make sense since said RNA species or cDNA therefrom and the reference amplified product or signal of said RNA species or cDNA therefrom extracted from non-cellular fractions of blood from a human group or population without said disease are different materials and are not comparable. Please clarify.

14. Claim 6 is rejected as vague and indefinite. Since claim 1 is not directed to a method for detecting a disease and does not amplify a tumor-associated extracellular RNA species in a non-cellular fraction of blood from a human, it is unclear why the overexpression of a tumor-associated extracellular RNA species in human blood plasma or serum can indicate that the disease is a neoplastic disease. Please clarify.

15. Claim 9 or 20 recites the limitation "the reference range RNA amount or concentration for said RNA species" in the claim. There is insufficient antecedent basis for this limitation in the claim because there is no phrase "a reference range RNA amount or concentration for said RNA species" before "the reference range RNA amount or concentration for said RNA species". Please clarify.

16. Claim 45 is rejected as vague and indefinite. Since claim 9 is not directed to a method for detecting a cancer and does not amplify a tumor-associated extracellular RNA species in human blood plasma or serum, it is unclear why the human can be determined to have cancer when the RNA species is a tumor-associated RNA. Please clarify.

17. Claim 46 is rejected as vague and indefinite. Since claim 9 is not directed to a method for detecting a cancer and does not amplify a tumor-associated extracellular RNA species in a non-

cellular fraction of blood from a human, it is unclear why the human can be determined to have cancer when the RNA species is a tumor-associated RNA. Please clarify.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1, 4, 5, 8, 9, 12, 20, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balazs *et al.,* (WO 90/09456, published on August 23, 1990) in view of Korneluk *et al.,* (US Patent No. 6,656,704, priority date: August 5, 1996).

Regarding claims 1 and 4, Balazs *et al.,* teach extracting total extracellular RNA from blood plasma or serum from a human (ie., a cancer patient), amplifying or signal amplifying quantitatively or qualitatively a portion of the extracted RNA or cDNA therefrom to produce an amplified product or signal, using primers or probes specific for a human RNA species or cDNA therefrom (ie., myc), and detecting quantitatively or qualitatively the amplified product or signal as recited in claim 1 wherein the amplified product is produced from a tumor related RNA or cDNA produced therefrom (ie., myc) as recited in claim 4 (see pages 4 and 14-24).

Regarding claims 5 and 8, Balazs *et al.,* teach extracting total extracellular RNA from a non-cellular fraction of blood from a human (ie., a cancer patient), amplifying or signal amplifying quantitatively or qualitatively a portion of the extracted RNA or cDNA therefrom to produce an amplified product or signal, using primers or probes specific for a human RNA

species or cDNA therefrom (ie., myc), and detecting quantitatively or qualitatively the amplified product or signal as recited in claim 5 wherein the amplified product is produced from a tumor related RNA or cDNA produced therefrom (ie., myc) as recited in claim 8 (see pages 4 and 14-24).

Regarding claims 9 and 12, Balazs *et al.,* teach extracting total extracellular RNA from plasma or serum from a human (ie., a cancer patient), a portion of which comprises a human RNA species and determining an amount or concentration of said human RNA species in the extracted portion of human blood plasma or serum as recited in claim 9 wherein the human has cancer as recited in claim 12 (see pages 4 and 14-24).

Regarding claims 20 and 23, Balazs *et al.,* teach extracting total extracellular RNA from a non-cellular fraction of blood from a human (ie., a cancer patient), a portion of which comprises a human RNA species and determining an amount or concentration of said human RNA species in the extracted portion of a non-cellular fraction of blood from a human as recited in claim 20 wherein the human has cancer as recited in claim 23 (see pages 4 and 14-24).

Balazs *et al.,* do not disclose comparing the detected amplified product or signal to a reference amplified product or signal of said human RNA species or cDNA extracted determined from plasma or serum from a human group or population without disease wherein the human RNA species extracted from human blood plasma or serum is determined to be overexpressed when the detected amplified product or signal from the human in an amount or concentration greater than the reference amplified product or signal of said RNA species or cDNA therefrom extracted from blood plasma or serum from a human group or population without said disease as recited in claim 1, comparing the detected amplified product or signal to a reference amplified

product or signal of said human RNA species or cDNA extracted determined from a non-cellular fraction of blood from a human group or population without disease wherein the human RNA species extracted from a non-cellular fraction of blood is determined to be overexpressed when the detected amplified product or signal from the human in an amount or concentration greater than the reference amplified product or signal of said RNA species or cDNA therefrom extracted from a non-cellular fraction of blood from a human group or population without said disease as recited in claim 5, and comparing the amount or concentration of said human RNA species from plasma or serum of said human to the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as recited in claim 9, and comparing the amount or concentration of said human RNA species from a non-cellular fraction of blood of said human to the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as recited in claim 20.

Korneluk *et al.,* teach to detect expression of hiap-1 in the Raji Burkitt's lymphoma cell line using RT-PCR and determine overexpression of hiap-1 by comparing with positive and negative controls (see column 26).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 or 5 or 9 or 20 by comparing the detected amplified product or signal to a reference amplified product or signal of said human RNA species or cDNA extracted determined from plasma or serum from a human group or population without disease wherein the human RNA species extracted from human blood plasma or serum is determined to be overexpressed when the detected amplified

product or signal from the human in an amount or concentration greater than the reference amplified product or signal of said RNA species or cDNA therefrom extracted from blood plasma or serum from a human group or population without said disease or by comparing the detected amplified product or signal to a reference amplified product or signal of said human RNA species or cDNA extracted determined from a non-cellular fraction of blood from a human group or population without disease wherein the human RNA species extracted from a non-cellular fraction of blood is determined to be overexpressed when the detected amplified product or signal from the human in an amount or concentration greater than the reference amplified product or signal of said RNA species or cDNA therefrom extracted from a non-cellular fraction of blood from a human group or population without said disease or by comparing the amount or concentration of said human RNA species from plasma or serum of said human to the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer or by comparing the amount or concentration of said human RNA species from a non-cellular fraction of blood of said human to the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer in view of the prior art of Balazs *et al.,* and Korneluk *et al.*. One having ordinary skill in the art would have been motivated to do so because Korneluk *et al.,* have shown to detect expression of hiap-1 in the Raji Burkitt's lymphoma cell line using RT-PCR and determine overexpression of hiap-1 by comparing with positive and negative controls (see column 26) and use of a reference amplified product or signal of said human RNA species or cDNA extracted determined from plasma or serum from a human group or population without disease as an experimental control or the use of a reference amplified

product or signal of said human RNA species or cDNA extracted determined from a non-cellular fraction of blood from a human group or population without disease as an experimental control or the use of the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as an experimental control or the use of the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as an experimental control during the process of performing the method recited in claim 1 or 5 or 9 or 20, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the experimental controls are needed to eliminate alternate explanations of experimental results and used to prevent the effects of one variable from being drowned out by the known, greater effects of other variables. One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claim 1 or 5 or 9 or 20 by using a reference amplified product or signal of said human RNA species or cDNA extracted determined from plasma or serum from a human group or population without disease as an experimental control or using a reference amplified product or signal of said human RNA species or cDNA extracted determined from a non-cellular fraction of blood from a human group or population without disease as an experimental control or using the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as an experimental control or using the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as an experimental control.

20. Claims 14 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balazs *et al.,* in view of Korneluk *et al.,* as applied to claims 1, 4, 5, 8, 9, 12, 20, and 23 above.

The teachings of Balazs *et al.,* and Korneluk *et al.,* have been summarized previously, *supra*.

Balazs *et al.,* and Korneluk *et al.,* do not disclose that the human is a human who has not been diagnosed with cancer as recited in claims 14 and 25.

However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 9 or 20 using a human who has not been diagnosed with cancer as recited in claim 14 or 25 in view of prior art of Balazs *et al.,* and Korneluk *et al.*. One having ordinary skill in the art would have been motivated to do so because use of the plasma or serum or non-cellular fraction from a different human for performing the method recited in claim 9 or 20, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

21. Claims 17, 18, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balazs *et al.,* in view of Korneluk *et al.,* as applied to claims 1, 4, 5, 8, 9, 12, 20, and 23 above.

The teachings of Balazs *et al.,* and Korneluk *et al.,* have been summarized previously, *supra*.

Balazs *et al.,* and Korneluk *et al.,* do not disclose that the group or population comprises humans of a specific sex or age group as recited in claims 17 and 28 and the group or population comprises humans who smoke as recited in claims 18 and 29.

However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 9 or 20 using the group or population comprising humans of a specific sex or age group as experimental controls as recited in claim 17 or 28 or using the group or population comprises humans who smoke as experimental controls as recited in claim 18 or 29 in view of prior art of Balazs *et al.,* and Korneluk *et al.*. One having ordinary skill in the art would have been motivated to do so because use of the plasma or serum or non-cellular fraction from a different group or population as an experimental control for performing the method recited in claim 9 or 20, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. No claim is allowed.

22. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Frank W Lu /
Primary Examiner, Art Unit 1634
July 2, 2008